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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/27/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/605,042	WU ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-10,12-16,25 and 28-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-10,12-16,25 and 28-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 July 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner. *see PTO-948*

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The instant application claims priority to a Provisional App. No. 60/108195 filed on 11/13/1998.

Election/Restrictions

In response to the amendment and applicant's arguments filed on 12/05/02 the restriction requirement issued on 11/05/02 has been withdrawn.

Claims 2-6, 11, 17-24, 26 and 27 are canceled.
Claim 47 is newly filed.
Claims 1 and 29 are amended.
Claims 1, 7-10, 12-16, 25, 28-47 are pending and were examined in this office action.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED.*

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 29-30 and 33-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,824,543. Although the conflicting claims are not identical, they are not patentably distinct from each other because an isolated DNA molecule comprising a kidney specific promoter (mouse uromodulin) operably linked to a heterologous DNA sequence as claimed in the instant application encompasses the subject matter "a recombinant nucleic acid construct comprising a mouse UP-II promoter operatively linked to a hetrologous gene wherein the promoter directs the expression of the heterologous gene product in the urothelium in vivo" as claimed in US '543.

Claims 29-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,001,646. Although the conflicting claims are not identical, they are not patentably distinct from each other because an

isolated DNA molecule comprising a kidney specific promoter (mouse or goat uromodulin) operably linked to a heterologous DNA sequence as claimed in the instant application encompasses the subject matter "a vector comprising a UP-II promoter operatively linked to a hetrologous gene encoding a selected biologically active molecule wherein the promoter directs the expression of the heterologous gene product in the urothelium" as claimed in US '646.

Claims 29-34 and 38-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. US 6,339,183. Although the conflicting claims are not identical, they are not patentably distinct from each other because an isolated DNA molecule comprising a kidney specific promoter (mouse or goat uromodulin) operably linked to a heterologous DNA sequence as claimed in the instant application encompasses the subject matter "a vector comprising a promoter construct linked to a heterologous DNA encoding a selected biologically active molecule wherein the promoter construct directs expression of the heterologous DNA to the urothelium so that the selected biologically active molecule expressed by the heterologous DNA is detected in urine" as claimed in US ''183. In addition the non-human transgenic mammals and the method for producing a recombinant biologically active polypeptide in a non-human transgenic mammal as claimed in the instant application clearly encompasses the "non-human transgenic mammals like mice, rat, cow, pig, sheep, goats, monkey and rabbits and method of producing a selected biologically active molecule in the urine of a non-human mammal" as claimed in US '183.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25, 29-30, 33-34, 36-41 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin J et al (PNAS 92:679-683, 1995).

The cited art teaches an expression vector (UPII-lacZ) comprising a mouse UPII (uromodulin, a kidney specific promoter) operably linked to β-galactosidase gene (heterologous DNA) see page 681, fig-4b, page 680, fig-1. The cited art further teaches mouse UPII genomic DNA that comprise the UPII promoter (page 680, fig-1). The cited art further teaches a method for making a transgenic mouse by microinjecting the pUPII-lacZ DNA construct into the fertilized mouse eggs (page 679, col.2 para.3). The cited art further teaches a transgenic mouse (non-human mammal), whose germ and somatic cells contain the UPII-lacZ transgene construct. In addition the cited art teaches the expression of transgene (lacZ) in the urothelium of the founder mice (page 682, fig-5).

The cited art clearly anticipate the invention as claimed because the composition and functions as claimed are presumed inherent. The composition is physically the same it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties."A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)

see MPEP § 2112.02. Even though the cited art only disclosed the expression an exogenous polypeptide (lacZ) in the urothelium, one ordinary skill in the art would had detected the lacZ excreted in the urine, since it is know in the art that uroepithelium is involved excretion of urine especially the uromodulin which regulated by uromodulin promoter (see Su et al J Immunolgy 158:3449-3436, 1997).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 8-16, 25, 28-29 and 38-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, **had possession of the claimed invention**.

The scope of invention as claimed encompasses any and all kidney specific promoters, any and all non-native apical surface membrane targeting sequences, any and all protease sensitive linkers, any and all protein having basolatral surface membrane targeting signals, any and all non-human transgenic mammals encoding any and kidney specific promoters that directs the expression of a heterologous polypetide in the urine.

At best the specification as filed only disclosed isolation of mouse and goat uromodulin promoter sequence (a kidney specific promoter). Furthermore the specification only disclose a transgenic mouse wherein the uromodulin promoter has been operatively linked to the human growth hormone coding sequences (spec. page 48, example-3). The specification further discloses two founder mice (UPII-hGH), which excrete hGH in their urine (page 51, lines 12-19). The specification only disclosed the glycosyl phosphatidylinositols (GPI) sequences present in uromodulin gene that directs the expression of uromodulin to the apical surface membrane in kidney cells (page 27, lines 6-24, fig-3). The specification further disclosed that the PIPLC is the only enzyme, which specifically cleaves the GPI linkage (page 30 lines 5-13).

The specification fails to disclose recombinant DNA molecules comprising all kidney specific promoters, all non-native apical surface membrane targeting sequences, all protease sensitive linkers, all protein having basolatral surface membrane targeting signals. In addition the specification fails to disclose a single non-human transgenic mammal that encodes a transgene comprising the above mentioned components so that the animal excretes any heterologous polypetide of interest in the urine the mammal.

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USP2d 1481 at 1483. In Fiddes, claims directed to a mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Considering the instant disclosure the specification only disclosed

mouse and goat uromodulin promoters, which does not encompasses the full breath of invention as claimed. In addition possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case a kidney specific promoter, apical surface membrane targeting sequences and basolatral surface membrane targeting sequences has been defined only by a statement of function that is only kidney specific which conveyed no distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

4. Claims 1, 7-10, 12-16, 25, 28-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA molecule comprising a mammalian uromodulin promoter operably linked to a fusion polypeptide comprising hetrologous DNA sequence encoding a heterologous polypetide containing the uromodulin GPI sequences for apical surface membrane targeting sequence, does not reasonably provide enablement for any DNA molecule that contains any and all kidney specific promoters, non-native apical surface membrane targeting sequences, protease sensitive linkers, modified basolatral surface membrane targeting signals and any and all non-human transgenic animals encoding the DNA molecules (as claimed) wherein the heterologous polypeptide of interest is produced in the urine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims.

Nature Of Invention:

The invention relates to a DNA construct and non-human transgenic mammals that produce a recombinant biologically active polypeptide in the urine using a kidney specific promoter.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses any and all kidney specific promoters, any and all non-native apical surface membrane targeting sequences, any and all protease sensitive linkers, any and all protein having basolatral surface membrane targeting signals, any

and all non-human transgenic animals encoding any and all kidney specific promoters that directs the expression of a heterologous polypetide in the urine.

The specification teaches that uromodulin is a kidney specific promoter (spec. page 16, line 21-27). The specification as filed further disclosed the isolation of mouse and goat uromodulin promoter sequences. Furthermore the specification only disclose a transgenic mouse wherein the uromodulin promoter has been operatively linked to the human growth hormone coding sequences (see spec. page 48, example-3). The specification further discloses two founder mice (UPII-hGH), which excrete hGH in their urine (page 51, lines 12-19). The specification only disclosed the glycosyl phosphatidylinositols (GPI) sequences present in uromodulin gene that directs the expression of uromodulin to the apical surface membrane in kidney cells (page 27, lines 6-24). The specification further disclosed that the PIPLC is the only enzyme, which specifically cleaves the GPI linkage (page 30 lines 5-13). In addition, the specification only characterized the Asn-lined glycosylation sites and GPI sites in rat mouse and human uromodulin amino acid sequences.

State Of Art And Predictability:

The state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. (Wood. Comp. Med. 50(1): 12-15, 2000, see page12). The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular

phenotype. These epigenetic effects can dramatically alter the observed phenotype and therefore can influence or later the conclusions drawn form the transgenic or knockout models (Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, see page 1425). The transgene expression and physiological consequences of transgene products in non-mouse mammals are not always accurately predicted among various species of mammals (Wall RJ Theriogenology 45:57-68, 1996). Transgene efficiency is low, and range from 1% in farm animals (cattle, sheep, pigs) to 3% in laboratory animals like rabbits, mice and rats (Wall, see page 61). Furthermore, the lack of understanding of essential genetic control elements make it difficult to predict the behavior of a transgene in any and all animals because the expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene (Wall, page 61-62). The cis acting elements of one species may interact with different transactivating factors in other species. For example, the introduction of human growth hormone transgene in mice results in mammoth mouse phenotype, where as expression of the same transgene in pig results in premature death of transgenic pigs. (Pursel VG et al J. Reprod Fert. Sup 40: 235-245 1990, see page 235, para.1).

Furthermore, many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, for example are the important factors that govern the expression of a

transgene. (Kappel et al. Current Opinion in Biotechnology 3:558-553 1992; see page 550, col.1, para. 3-4, page 548, col.2 para.2). In addition considering the urine-based bioreactor system, the art the time of filing teaches that the function of mammalian kidney is complex wherein the excretion of a gene product of interest in kidney can only be achieved by gene expression in the ascending limbs of Henle' sloop in kidney. Furthermore only the modified uromodulin promoter that contains exon 1 and a part of exon 2 has been known to provide kidney specific expression of reporter gene in transgenic mice that leads to production of the recombinant protein in urine (Zbikowska et al Biochem J 365:7-11, 2002, see abstract, page 7 col.1).

Quantity Of Experimentation Required:

Considering the unpredictability the state of transgenic art and limited guidance provided in the instant specification to make any and all non-human transgenic mammals comprising any and all kidney specific promoters that directs the expression of gene product of interest with further modification (as claimed) in the urine are not considered routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation required would include identification of kidney specific promoters that leads the expression of gene of interest to the ascending limbs of Henle' sloop in the kidney so that gene product can be secreted in the urine. The undue

experimentation required would further include the modification of the gene construct so that gene product of interest is effectively excreted from the apical surface membrane in kidney. The undue experimentation required would further include the characterization of a heterologous polypeptide of interest for the presence of apical or basal sorting signals before making the recombinant DNA construct. The undue experimentation would further include making and testing any and all non-human transgenic mammals comprising the modified kidney specific expression system as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 8, 13, 15, 16, 34 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is indefinite because it is unclear what is "one or more non-native sites for glycosylation at predicted β-turns" in this context.

Claim 13 recites the limitation "said fusion polypeptide" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 15 is indefinite because it is unclear what is "disposed 3' of " in this context.

Claim 16 is indefinite because it is unclear how the "basolatral surface membrane targeting signals native to said hetrologous polypeptide is inactivated or deleted" in this context.

Claim 34 is indefinite because it is unclear what is "a fragment thereof "in this context.

Claim 47 is indefinite because it is unclear how the "basolatral surface membrane targeting signals are inactivated or deleted" in this context.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

SUMESH KAUSHAL
PATENT EXAMINER